

be transmitted to internal viscera, and if sufficiently strong produce pathologic function. On this basis the relief of a nerve irritation caused by scoliosis, as discussed in Doctor Ussher's paper, may be a means of relieving pathologic function in internal viscera.

✱

LEWIS GUNTHER, M. D. (913 Pacific Mutual Building, Los Angeles).—In 1928 Dr. William J. Kerr and the writer showed that osteo-arthritis of the spine could be the cause of pain at the periphery which closely simulated visceral disease. Confusion in diagnosis of visceral disease becomes a natural consequence, since the distribution of the pain in osteo-arthritis follows the dermatomes of the roots of the spinal nerves, and the Head zones of visceral pain also occur within the distribution of the roots of the spinal nerves. Methods for the clinical recognition of the pain of nerve root origin were described.

The medical literature has been slowly but increasingly affording recognition of the painful disturbances associated with spinal arthritis. However, as Doctor Ussher has pointed out, the possibility of visceral disturbances being reflexly originated by pathologic processes in the spine has received little or no consideration.

The possible sensory reflex reactions in the viscera, according to Doctor Ussher, would be described by the patient as "colicky pain, a sense of fullness, inability to draw a full breath, gas cramps, etc." He also demonstrated by his thorough studies that such symptomatology was associated with and could be attributed to pylorospasm, spastic states of the colon, or to partial ureteral obstructions also due to spasm of the ureter. It is a striking feature indeed (in all but one of the case histories presented) that although the word pictures painted by his patients were descriptive of symptoms that are more commonly associated in our minds with disease of the hollow viscera the distribution of the subjective painful sensory disturbances was along the dermatomes of the roots of the spinal nerves, and by their distribution they constituted a radiculitis.

In our original descriptions of the radicular syndrome are also to be found terms often used by patients in describing symptoms of visceral disease, *viz.*, burning, tingling, heaviness, pressure, stabbing pain, and gas. These we described under the heading of "nerve root paresthesias." These were distributed strictly according to spinal root dermatomes. Their frequency of occurrence, however, showed a much smaller incidence than the symptoms purely descriptive of root pain. In our effort to attain an understanding of the patient's language when telling of his symptoms, we were satisfied at the time to place the group of terms descriptive of visceral disease under the heading of a radiculitis because they followed the typography of the spinal nerve roots. According to our major premise, sensory disturbances which show by their distribution that the primary disease process is in the spinal root and not in the tracts, nuclei of the cord, or in a peripheral nerve trunk, constitute a radiculitis rather than the viscerosensory reflex of visceral disturbances.

Doctor Ussher's work has shown that sensory disturbances at the periphery of a radicular distribution may also be concomitant with spasms of the various hollow abdominal viscera. How is one to differentiate pure nerve root sensory pain and pure visceral disease pain in nerve root areas referred through Head zones from nerve root pain due to spinal disease and associated with spasms within the viscera which also give rise to symptoms?

Our criterion for the differentiation of radicular pain due to disease in the spine from Head zones of referred pain due to a diseased viscus which may also be referred within the same nerve roots as the radicular pain are as follows: Whether one accepts the viscerosensory reflex theory of Mackenzie or the peritoneocutaneous reflex theory of Morley, the fact nevertheless remains that pure Head zone pain which is associated with visceral disease rarely involves the entire cutaneous distribution of the nerve root dermatome.

On the other hand, the radicular pain of spinal disease always involves the entire distribution of the spinal dermatome. The Head zones of subjective sensations in visceral disease are poorly defined, whereas the radicular pains of spinal disease are accurately delineated. Memory for the former is poor, and sharp for the latter. The patient can accurately delineate radicular pain even many years after it has subsided. To this differentiation now must be added Doctor Ussher's syndrome. Doctor Ussher's spinovisceral syndrome describes symptoms commonly descriptive of visceral disease and root pain are associated with spinal curvatures and are concomitant with spasms of the hollow viscera. These symptoms depend on the nerve roots that are involved. Doctor Ussher is to be congratulated for calling the attention of the profession to this syndrome.

✱

DOCTOR USSHER (Closing).—Since compiling the above report of cases, presenting visceral symptomatology related to spinal curvatures, twelve new cases have been observed in our group. These, we believe, conform to the postulates of the "viscerospinal syndrome" and offer still further data, especially in the field of bronchospasm and asthma. This series will be discussed later.

A question was asked by Doctor Gunther as to the differentiation between pure nerve root sensory pain due to spinal disease and pure visceral disease pain referred to corresponding spinal segments. I believe this differentiation may often be made by a careful neurologic examination assisted by roentgenograms of the spine. In any case visceral pathology must be ruled out by the usual methods of differential diagnosis.

PERNICIOUS ANEMIA—MAINTENANCE DOSE OF LIVER EXTRACT NECESSARY*

By HENRY GIBBONS, III, M. D.
San Francisco

APPROXIMATELY two years ago the value of the treatment of pernicious anemia by intramuscular injections of liver extract became generally recognized.^{1, 2} The question arose concerning the maintenance dose in the average case. Is it true, as suggested,³ that one injection a month is sufficient for most cases? Just how intensively should certain cases be treated? It was believed that regular intramuscular injections of liver extract were much less expensive for the patient than liver extract by mouth. This method is certainly less objectionable than eating daily portions of liver.

PROCEDURE USED IN THIS STUDY

In order to evaluate the various new forms of treatment of pernicious anemia, the following course was adopted. In January, 1932, all cases of pernicious anemia being treated in the Lane Out-Patient Medical Clinic were instructed to stop eating liver, kidneys, and sweetbreads and not to take any more liver extract by mouth. Arrangements were then made to have the patients report at frequent intervals for a red blood count and a hemoglobin determination. Whenever the hemoglobin fell below 80 per cent (Sahli), an injection

* From the department of medicine, Stanford University Medical School.

* This study supported, in part, by a grant from the Rockefeller Fluid Research Fund of the School of Medicine, Stanford University.

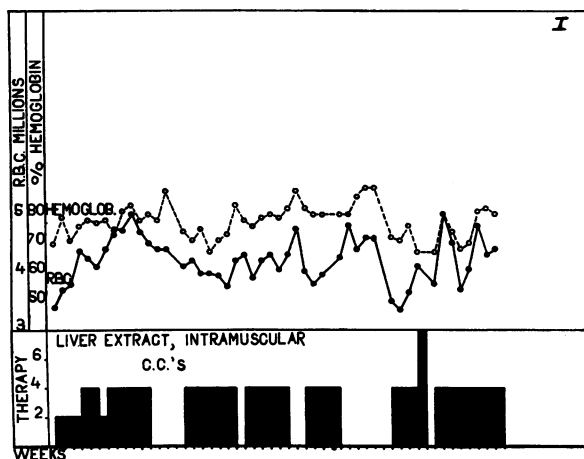


Chart 1.—Weekly record of red blood count and hemoglobin determinations in a patient receiving intramuscular injections of Lilly's liver extract. Unless 4 cubic centimeters are given once a week a normal blood count is not maintained.

of liver extract was given intramuscularly. Of course, if any symptoms of weakness or numbness of the extremities developed, this plan could not be so closely adhered to. In two cases, "Extralin" by mouth was given.

GROUPING OF THE PATIENTS STUDIED

Twenty-one cases were followed. In following these patients, one cannot help getting the impression that there is a natural reservoir of a certain potent material in the body which must be kept filled to the brim at all times, else symptoms of pernicious anemia develop.

Three of these patients were shown to require regular weekly injections of Lilly's Liver Extract 343 for intramuscular injection in 4 cubic centimeter amounts. Chart 1 illustrates the response of one patient of this group and how this fact is arrived at. Two cubic centimeters weekly injections do not seem quite adequate at the onset. The dose, therefore, is increased to 4 cubic centimeters a week. After eleven weeks of regular injection, these are stopped because the blood count and hemoglobin are normal. Three weeks later the hemoglobin drops below normal and injections are resumed. It will be noted that there then is a slow but gradual rise of blood to normal again. Subsequently, whenever treatment is stopped there is this same sequence of events. The conclusion is that 4 cubic centimeters a week is the minimum on which this patient can get along. Whether 8 cubic centimeters every two weeks are just as effective has not been determined. On this regular weekly treatment the blood count and hemoglobin have remained normal for six weeks.

Two other patients receiving this same form of treatment have not required liver injections very often. At times their hemoglobin is below 80 per cent (Sahli); nevertheless they have no symptoms. A prompt response following each injection of 4 cubic centimeters always occurs. In the case shown here (Chart 2 *a*), the shortest interval between injections is five weeks, the longest thirteen weeks. It appears that one injection a month is quite sufficient as a maintenance dose. This

cannot be carried out any longer in this case because of severe reactions coming on one-half hour after the last two injections and lasting for from one-half to one hour. The signs and symptoms of the reaction are nausea, vomiting, sweating, flushing of the skin, rapid pulse, fall in blood pressure, and weakness. A similar reaction occurred in one other case. It is noteworthy that in both instances the injections are more widely spaced than in the other cases treated. This suggests an allergic reaction due to protein sensitization from previous injections. This patient is now doing well on six capsules of "Extralin" daily.

The next group of four cases were followed for from six to twelve months without the need of any liver whatsoever. They are evidently in a remission. They will be carefully followed for the onset of a relapse. Chart 2 *b* is a record of one case.

Four other patients have neurologic symptoms. The purpose is to treat them intensively. One patient reports two times weekly for an injection of 8 cubic centimeters of Lilly's Liver Extract 343. A longer interval between injections has been tried, but without success; weakness of legs is noticed. Another patient does well on 2 cubic centimeters every two weeks. Another receives

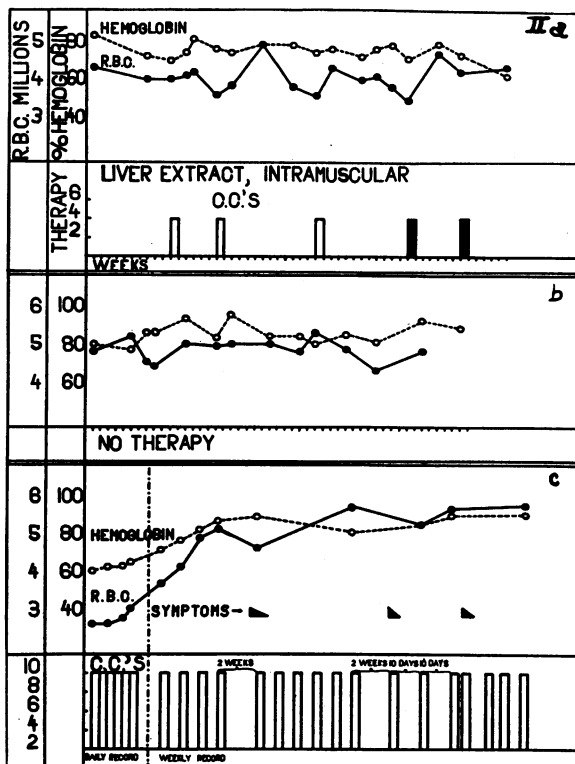


Chart 2 (a).—In this patient 4 cubic centimeters of liver extract produces a response in blood count in all except the last injection, which is complicated by a histamin-like reaction one-half hour afterward. One injection a month will apparently maintain a normal blood count. Because of reaction to injections, the patient is now taking "Extralin" by mouth.

Chart 2 (b).—This patient is in a remission and does not require any liver to maintain a normal blood count.

Chart 2 (c).—This patient with neurologic symptoms responds well to intensive intramuscular liver therapy at the beginning. Although blood count remains normal, symptoms recur unless regular weekly injections of 10 cubic centimeters of liver extract are given.

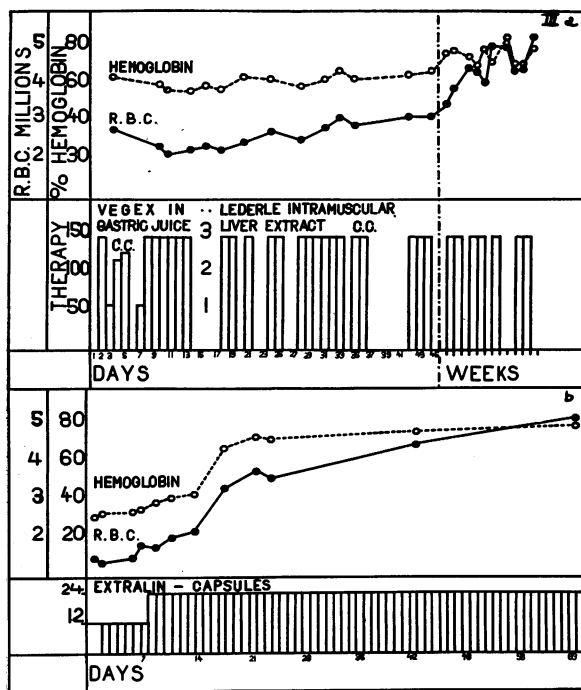


Chart 3 (a).—This patient has no response to pre-digested vegex by mouth and responds very slowly to frequent injections of 3 cubic centimeters of Lederle's liver extract. It appears as though one injection a week will maintain a normal blood count.

Chart 3 (b).—Twelve capsules of "Extralin" a day are not sufficient to produce a response in this patient. Twenty-four capsules daily do. Now that a normal blood level has been reached, the maintenance dose is probably much less than twenty-four capsules a day, however.

3 cubic centimeters of Lederle's liver extract every week, with marked improvement in weight and strength. Chart 2 c illustrates the response of a woman of forty-nine who developed pernicious anemia and combined sclerosis in July, 1932. A satisfactory response is obtained with intensive intramuscular treatment at the onset. Then it is found that 10 cubic centimeters a week are necessary to keep the patient symptom free. When a two-week interval is attempted, she begins to feel weak and has numbness of the lower extremities. Even a ten-day interval seems inadequate. The patient is now doing very well on weekly injections. It will be noted that the blood count is no final index of treatment in a case with neurologic disturbances.

Two other patients did not respond well to large amounts of liver by mouth—the so-called "liver-resistant" cases. They have responded slowly to intramuscular injections. In the case here illustrated (Chart 3 a), twelve days' trial of Castle's⁴ formula of 15 grams of vegex digested in 150 grams of gastric juice does not cause any response. Injections of 3 cubic centimeters of Lederle's liver extract nearly every day for about three weeks produces a gradual response. It seems now, from weekly observation, that 3 cubic centimeters a week of this extract is the maintenance dose here.

The last two patients received only Extralin by mouth. Twelve capsules a day are inadequate, as shown in the first week's treatment (Chart 3 b), but twenty-four capsules daily produce results.

It is difficult to determine the relative potency of liver and the various liver preparations because, as Minot⁵ says, at present there is no satisfactory way of defining a unit of potent material. It is said that one vial of oral liver 343 when taken, although an extract of 100 grams of fresh liver, is actually only equivalent to about 80 grams in potency. Minot⁵ has made the statement that parenteral liver extract (343) is equivalent in its effect to at least thirty times the amount of fresh liver, from which it is extracted. Thus, extract from 50 grams of fresh liver when given intramuscularly should give a response equal to 1500 grams by mouth. Gänsslen⁶ gives comparative doses, which seem to indicate that the potency of the extract is even greater—fifty or sixty times that of fresh liver by mouth. In a rough way the potency has been confirmed in the first case. The patient represented in Chart 1 was doing well on one vial of 343 by mouth daily before starting intramuscular treatment. He now does well on 4 cubic centimeters of liver extract intramuscularly each week. Now, one vial a day = seven vials a week = about 600 grams of fresh liver. Thus, the response from 4 cubic centimeters liver extract, an extract from 20 grams of fresh liver, is equal to the response from 600 grams of liver by mouth or about thirty times greater than if taken orally.

A rough estimation of the potency of "Extralin" can be obtained by the following reasoning. Minot stated⁷ that "on the average when liver extract derived from 500 to 600 grams of liver has been fed daily to patients with less than two million red blood cells per cubic millimeter of blood, it has increased the concentration of these cells about 2.5 million per cubic centimeter in thirty

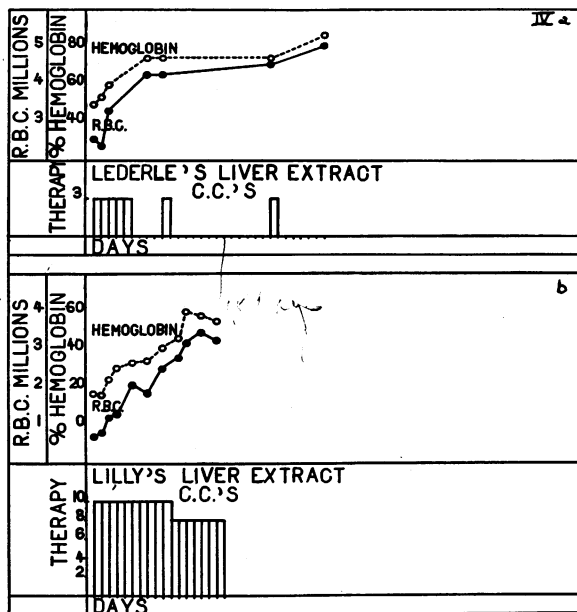


Chart 4 (a).—This illustrates response of patient receiving 3 cubic centimeters of Lederle's liver extract for comparison with response to one receiving 10 cubic centimeters of Lilly's liver extract in Chart 2 (c). Both start out at the same blood level and receive six and eight injections respectively, indicating that Lederle's extract of 100 grams of liver is not two times as strong as Lilly's extract of 50 grams of liver.

Chart 4 (b).—Normal blood response and example of beginning treatment in a case of pernicious anemia.

days." This response is obtained (Chart 3 *b*) in the patient who received twenty-four capsules of "Extralin" daily. Twenty-four capsules of "Extralin" are, therefore, roughly equivalent to 500 grams of liver.

In addition, it has been noted that the response of a patient to 3 cubic centimeters of Lederle's liver extract (which is an extract from 100 grams of fresh liver) does not seem to be much greater than 10 cubic centimeters of liver extract 343 (Chart 4 *a*). In this case, Chart 4 *a*, a rise of two million red blood cells occurs as a result of six injections of 3 cubic centimeters of Lederle's liver extract. Eight injections of 10 cubic centimeters of Lilly's liver extract cause a similar response in the patient whose record is shown in Chart 2 *c*. From this comparison it does not seem that 3 cubic centimeters of Lederle's extract (an extract from 100 grams of liver) is twice as potent as Lilly's extract (an extract from 50 grams of liver). The reason for this must be that "when extracts are made there is considerable loss of potent material, and the purer the potent material has been rendered the greater the loss of active principle."⁵ The variation of response of individuals is a factor, also, and therefore the absolute relative potency cannot be determined from these observations.

RELATIVE VALUES WHICH ARE SUGGESTED

From the data gathered in the treatment and observation of this small series of cases, the following relative values are suggested.

One vial of Lilly's Liver Extract 343, intramuscular, containing 10 cubic centimeters of extract from 50 grams of fresh liver is equivalent to 1500 grams, or three pounds of fresh liver toward producing a response in a case of pernicious anemia. One vial of Lederle's liver extract may possibly be equal to this in potency. It must be "remembered that the fact that any particular extract is derived from a given amount of liver does not guarantee that it retains the potency of that amount of liver." Seventy to eighty capsules of "Extralin" are equivalent to three pounds of liver. These in turn are equivalent to fifteen vials of Lilly's 343 by mouth.

An important point in the beginning of treatment of a patient with pernicious anemia now presents itself. It has been observed that 500 grams of fresh liver will produce a rise of 2.5 million red blood cells per cubic millimeter in thirty days. Ten daily injections of 10 cubic centimeters of 343 is equivalent to this amount of liver. A rise of 2.5 million red blood cells has been produced in ten days by this form of treatment (Chart 4 *b*). Therefore, intensive therapy of at least ten injections of Lilly's 343 seems the best initial treatment for all cases of pernicious anemia. When the blood count becomes normal the case then becomes an individual problem in regard to a maintenance dose.

The relative cost of materials is as follows: Three pounds, 1500 grams, of liver usually cost about \$1.80. Fifteen vials of oral 343, its equivalent, cost \$3.75. One bottle of eighty-four "Ex-

tralin" capsules costs \$3.50; this is equivalent to a little over three pounds of liver. One vial of 343 costs \$1.75, and one vial of Lederle's liver extract costs \$1.10. So, intramuscular liver extract is the cheapest except that additional cost to the patient for treatment must be taken into consideration unless the patient is able to administer the substance himself. Unless this is so, fresh liver is really the cheapest form of treatment. Because of the undesirability of constantly taking liver, the oral preparations have been substituted. "Extralin," also, is very satisfactory. When a patient with pernicious anemia has attained a normal blood picture, being free from neurologic disorders, twelve or even six capsules a day will probably be a sufficient maintenance dose.

The possible explanation of the variation of the maintenance dose in pernicious anemia is that the patient himself produces variable amount of effective substance at different times. This is known to be so from old observations before the days of specific treatment when there were relapses because of depletion of the effective substance, followed by remissions.

CONCLUSIONS

1. No patients in this group have failed to respond to intramuscular liver therapy.
2. Intensive intramuscular liver therapy at the onset seems desirable, although not absolutely necessary, in all cases of pernicious anemia.
3. There is no uniform maintenance dose for all cases, but each patient should be treated as an individual problem and an effort made to give enough potent material at sufficiently frequent intervals to maintain an optimum nutritional state.²
4. This can most conveniently be accomplished by prescribing capsules of "Extralin" and, since the actual "maintenance dose" is quite difficult to determine accurately, it is more practicable to give a little larger dose than is absolutely necessary.
5. Reactions have occurred following intramuscular injections in two patients in whom the injections have been widely spaced.

Stanford Hospital, Clay and Webster Streets.

REFERENCES

1. Strauss, M. B., Taylor, F. H. L., and Castle, W. B.: Intramuscular Use of Liver Extract, *J. A. M. A.* (Aug. 1), 97:313, 1931.
2. Wilkinson, J. F.: Injections of Highly Purified Liver Preparations in Pernicious Anemia, *Lancet* (Oct. 10), 2:791, 1931.
3. Strauss, M. B., and Castle, W. B.: Parenteral Liver Therapy in the Treatment of Pernicious Anemia, *J. A. M. A.* (May 7), 98:1620, 1932.
4. Strauss, M. B., and Castle, W. B.: The Nature of the Extrinsic Factor of the Deficiency State in Pernicious Anemia and in Related Macrocytic Anemias, *New England Medical Jour.* (July 14), 207:55, 1932.
5. Minot, George R.: The Importance of the Treatment of Pernicious Anemia on a Quantitative Basis, *J. A. M. A.* (Dec. 3), 1932.
6. Gänsslen, M.: Ein hochwirksamer injizierbaren Leberextrakt, *Klin. Wochenschrift* (Nov. 8), 9:2099, 1930.
7. Minot, G. R., Cohn, E. J., Murphy, W. P., and Lawson, H. A.: Treatment of Pernicious Anemia with Liver Extract—Effects on the Production of Immature and Mature Red Blood Corpuscles, *Am. J. Med. Sc.* (May), 175:599, 1928.